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(71) Applicant(s)

**Pharmaceutical Industry Technology and
Development Center
(Incorporated in Taiwan)
5F No 101, Lane 169 Kang Ning St, Hsi Chih City,
Taipei Hsien, Taiwan**

(72) Inventor(s)

**Feng-Nien Ko
Chien-Jen Shih
Je-Yie Lin
Pey-Chyi Wu
Mo-Chi Cheng**

(74) Agent and/or Address for Service

**Beresford & Co
2-5 Warwick Court, High Holborn, LONDON,
WC1R 5DH, United Kingdom**

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(54) Abstract Title

Composition for the treatment of peptic ulcer comprising American ginseng

(57) The invention discloses a pharmaceutical composition for preventing and/or treating peptic ulcer, including American ginseng or the extract thereof, and a method for preparing American ginseng extract, said method including extracting American ginseng with water or ethanol aqueous solution, and then ultrafiltrating, dialyzing, precipitating with ethanol, or performing reverse phase chromatography to obtain various fractions of extract with anti-peptic ulcer effect.

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TITLEANTI-ULCER PHARMACEUTICAL COMPOSITION AND THE PREPARATION
THEREOF

5

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to pharmaceutical compositions useful for the prevention and/or treatment of peptic ulcer diseases. More particularly, it relates to the use of American ginseng or the extract thereof as the active ingredient for the prevention and treatment of peptic ulcer diseases.

Description of the Related Arts

15

American ginseng (*Panax quinquefolium* L.) is one species of Araliaceae, which is the North American variety of ginseng native to the United States and Canada. The *Panax* plants in Araliaceae, such as *Panax ginseng*, *Panax quinquefolium*, *Panax pseudo-ginseng* etc, have been used as a form of tonic in Chinese medicine for a long period of time, and *Panax ginseng* is traditionally considered a valuable medicinal material in China, Japan and Korea. After harvesting, *Panax ginseng* with good quality is generally treated with boiling water or steam to give red ginseng.

25 *Panax ginseng* which has been dried by hot air or sunlight is called white ginseng or unprocessed ginseng. The American ginseng is an herbaceous perennial and its root is mainly used as a nutritious tonic agent. Its morphology is similar to *Panax ginseng*, but has less fiber-like or lateral roots.

30 At present, the American ginseng is artificially cultivated

in the United States, Mainland China and Russia. Many reports have shown some components of American ginseng are similar to *Panax ginseng*, including several kinds of ginseng saponins, oligosaccharides, volatile oils, amino acids, vitamins and trace elements. It is traditionally believed that both American ginseng and *Panax ginseng* possess effects of increasing physical strength, nourishing and preserving health, and prolonging life. Thus, they are regarded as mild tonics used for daily dietary or medicinal remedy.

Recently, a number of scientific reports show that the American ginseng indeed possesses a variety of physiological or pharmaceutical activities, including anti-aging (Xiao P.G. et. al., 1993, *Journal of Ethnopharmacology* 38(2-3):167-75); preventing atherosclerosis and hyperlipidemia (Li J. et. al., 1999, *Life Science* 64(1):53-62); protecting liver from injury (Yoshikawa M. et. al., 1998, *Chemical and Pharmaceutical Bulletin* 46(4):647-54); enhancing the function of cardiovascular system (Kwan C. Y., 1995, *Clinical and Experimental Pharmacology and Physiology-Supplement* 1:S297-9; Yang S., 1992, *China Journal of Chinese Material Medica* 17(9):555-7 and US Patent No. 4,708,949); preventing memory dysfunction and dementia (Benishin C. G., 1991, *Pharmacology* 42(4):223-9; Li Z. et. al., 1999, *Journal of Pharmacy and Pharmacology* 51(4):435-40; Lewis R. et. al., 1999, *Phytotherapy Research* 13(1):59-64); decreasing hyperglycemia (Oshima Y. et. al., 1987, *Journal of Natural Products* 50(2):188-90; Martinez S. and Staba E. J., 1984, *Japanese Journal*

of *Pharmacology* 35(2):79-85); inhibition of breast cancer cells (Duda R. B. et. al., 1996, *Annals of Surgical Oncology* 3(6):515-20); enhancing physical strength; antiviral activity (US Patent No. 5,071,839);
5 anti-oxidation; decreasing the side effects of anticancer chemotherapy and radiotherapy (US Patent No. 4,945,115); modulating gastric digestion (Yuan C. S. et. al., 1998, *American Journal of Chinese Medicine* 26(1):47-55); and increasing the immune function (US Patent No.
10 4,795,742) etc.

Recently, the population with gastrointestinal diseases has been increasing, especially in highly developmental countries. The causes of peptic ulcers include unrelieved daily pressure; excessive alcohol irritation; the side
15 effects of drugs, such as aspirin or non-steroid anti-inflammatory drugs; or *Helicobacter pylori* infection. The predominant drugs used to treat peptic ulcers include muscarinic antagonists, such as methscopolamine bromide; H₂ blockers, such as
20 cimetidine; antacids, such as aluminum hydroxide or magnesium hydroxide; H⁺/K⁺ ATPase inhibitor, such as omeprazole; anti-bacterial drugs, such as admixture of amoxicillin and metronidazole. Such drugs may be classified into two categories: one is used for
25 physical protection of gastric mucosa to mitigate the irritation of the gastric acid to the mucosa ulcer site; the other is used for chemically inhibiting the secretion of the gastric acid, to avoid ulceration produced from excessive gastric
30 acid erosion. The prevalence of peptic ulcers and

their high rate of recurrence may be due to patients' life style or seasonal change and many patients repeatedly suffer from peptic ulcers. Thus, there is a need for a safe, mild and effective drug for
5 treating and preventing peptic ulcers.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide pharmaceutical compositions which are effective in
10 preventing and/or treating peptic ulcer diseases, comprising an effective amount of American ginseng and/or the extract thereof, and a physiologically or pharmaceutically acceptable carrier.

An additional object of the present invention is to
15 provide a process of preparing the extracts of the American ginseng described above, comprising the steps of (a) extracting American ginseng with a solvent with a polarity higher than 0.88 to obtain an extract; (b) filtering the extract to obtain a filtrate; and (c) centrifuging the
20 filtrate to obtain a supernatant (total extract).

The preparation process according to the present invention may further comprise the means of ultrafiltrating, dialyzing, precipitating with ethanol, or performing reverse phase chromatography, to obtain certain fractions of
25 American ginseng extract.

Another object of the present invention is to provide methods for preventing and/or treating a patient suffering from peptic ulcer, comprising administering an effective amount of American ginseng and/or the extracts thereof to
30 said patient.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a process of preparing the pharmaceutical compositions comprising American ginseng or the extract thereof. First, American ginseng is extracted with a solvent with a polarity higher than 0.88 to obtain an extract. Suitable solvent includes water, ethanol, methanol or the mixtures thereof, preferably water or ethanol, and more preferably 10% ~ 80% ethanol aqueous solution. Next, the extract is filtered to remove plant residues, and then centrifuged to remove microparticles and impurities. The resulting supernatant (total extract) is concentrated into an appropriate concentration, and then further treated by one or more of the following processes: ultrafiltrating, dialyzing, precipitating with ethanol, or performing reverse phase chromatography, to obtain various fractions of American ginseng extract.

In the process described above, ultrafiltrating is a step in which the total extract is filtered by an ultrafiltration membrane with molecular weight cut off 1,000 or 3,000 to give a retentate and a filtrate. Dialyzing is a step in which the total extract is dialyzed by a membrane or dialysis bag with molecular weight cut off 500 to remove smaller molecules. Precipitating with ethanol is a step in which the filtrate obtained from ultrafiltration is concentrated to dryness and then dissolved with 50% ~ 100% ethanol to obtain the soluble portion. Performing reverse phase chromatography is a step in which the filtrate obtained from ultrafiltration is loaded onto a reverse phase polyaromatic resin column, such as Diaion HP-20 (Sigma, Cat.

No. I-3605), to elute the active fraction of American ginseng extract.

All American ginseng extracts obtained from various processes of the present invention possess an anti-peptic
5 ulcer effect. Moreover, these extracts may be added to a physiologically acceptable carrier and/or formulated with a pharmaceutically acceptable excipient to obtain a pharmaceutical composition which is effective in treating or
10 preventing peptic ulcers. The term "peptic ulcer" used hereinbefore and hereinafter refers to gastric ulcers and/or duodenal ulcers.

Without intending to limit it in any manner, the present invention will be further illustrated by the following examples which are associated with the design of
15 the extraction step(s) and the assessment of pharmacological activity.

EXAMPLE 1

2,000 ml of deionized water was added to 200 g of
20 chopped American ginseng and then heated to boiling and further refluxed for 1 hour. The decoction was filtered through sieve gauge No. 200 (sieve pore 0.074 mm), and the filtrate (first filtrate) was collected. An additional 2,000 ml of deionized water was added to the residue of the American
25 ginseng described above, and was refluxed and filtered as described above to give the second filtrate. These two filtrates were combined and centrifuged at 10,000 rpm for 30 minutes to remove microparticles and impurities. The supernatant (total extract) was then filtered through the
30 ultrafiltration membrane with molecular weight cut off 1,000

(Amicon, Cat. No. S1Y1) to remove substances with molecular weight less than 1,000 dalton. The retentate containing substances with molecular weight greater than 1,000 dalton was concentrated under reduced pressure to give the extract I. The filtrate containing substances with molecular weight less than 1,000 dalton was concentrated to dryness, and then 90% ethanol solution was added to dissolve those substances. The ethanol solution was filtered (Advantec No. 2) to obtain the soluble portion, and the resulting soluble portion was added into the extract I described above. The mixture was concentrated under reduced pressure to give the extract II.

EXAMPLE 2

The total extract described in EXAMPLE 1 was treated through an ultrafiltration membrane with molecular weight cut off 3,000 (Amicon, Cat. No. S1Y3) to remove substances with molecular weight less than 3,000 dalton. The retentate containing substances with molecular weight greater than 3,000 dalton was concentrated under reduced pressure to give the extract III. The filtrate containing substances with molecular weight less than 3,000 dalton was loaded onto a column packed with Diaion HP-20 resin (Sigma, Cat. No. I-3605). The column was first eluted with deionized water until the eluate was colorless, and then eluted with 95% ethanol and the eluate was collected. The 95% ethanol eluate was added into the extract III described above. The mixture was concentrated under reduced pressure to give the extract IV.

EXAMPLE 3

The total extract described in EXAMPLE 1 was loaded in a dialysis bag with molecular weight cut off 500 (Spectra/Por®, Cat. No. 131 057). Both ends of the bag were
5 sealed with clamps. The bag was placed in a bucket contained deionized water, in which the ratio of the supernatant and deionized water was 1:10. The total extract was dialyzed at 4°C with stirring thrice each for 20 hours. The solution remaining in dialysis bag was collected and
10 concentrated under reduced pressure to give the extract.

EXAMPLE 4

1,000 ml of 80% ethanol solution was added to 100 g of chopped American ginseng and was heated to boiling and further
15 refluxed for 1 hour. The decoction was filtered through sieve gauge No. 200, and the filtrate (first filtrate) was collected. An additional 1,000 ml of 80% ethanol solution was added to the residue of the ginseng and extracted as described above, to give the second filtrate. These two
20 filtrates were combined and concentrated under reduced pressure to give the extract V.

EXAMPLE 5

Assessment of the pharmacological activity of anti-peptic
25 ulcer:

The anti-peptic ulcer activity of American ginseng was assessed using the methods described by Robert A. et. al. (1979, *Gastroenterology* 77:433-443), and Takagi I. and Okabe S. (1968, *Japan J. Pharmacol.* 18:9-18),
30 which is summarized below.

(1) The assessment of stress-induced ulcer:

Male Long Evans rats, weighing 150 ± 20 g, were administered American ginseng extracts orally after being fasted for 18 hours, while the control rats were

5 administered the same volume of distilled water orally.

After 1 hour, the rats were placed in a holder and partially immersed in water at $22 \sim 24^{\circ}\text{C}$ for 4 hours. The rats were then sacrificed and their stomachs were opened along the greater curvature for evaluation of the degree of ulceration.

10 Gastric ulceration was scored according to an arbitrary system:

0 = no bleeding

1 = spot bleeding

15 2 = slight bleeding

3 = severe bleeding and half stomach bloodstained

4 = very severe bleeding and entire stomach
bloodstained

Table 1. Effect of American ginseng extracts on stress-induced ulcer in rat.

Treatment	Dose (g/kg)	N	Inhibition (%) ^a
Total Extract	4	10	27.5±2.4
Extract I	4	10	42.5±3.6
Extract II	4	6	37.5±5.1
Extract III	4	10	42.5±3.6
Extract IV	4	6	51.2±3.8
Extract V	4	4	37.5±6.3

a: The inhibition rate (%) is calculated by the following equation:

$$[(\text{score of control animal}) - (\text{score of experimental animal})] / (\text{score of control animal}) \times 100\%.$$

All the ulcer scores of the control rats were 4.

(2) The assessment of ethanol-induced ulcer:

Male Long Evans rats, weighing 150±20 g, were administered American ginseng extracts orally after being fasted for 18 hours, while the control rats were administered the same volume of distilled water orally. After 15 minutes, the rats were administered 1 ml of absolute ethanol. After 1 hour, the rats were sacrificed and gastric ulceration was scored according to an arbitrary system:

- 0 = no lesions
 1 = hyperaemia
 2 = one or two slight lesions
 3 = more than two slight lesions or severe lesions
 4 = very severe lesions

Table 2. Effect of American ginseng extract on ethanol-induced ulcer in rat.

Treatment	Dose (g/kg)	N	Inhibition (%) ^a
Total Extract	4	10	50.0±0.0
Extract I	4	10	50.0±0.0
Extract II	4	6	45.8±3.8
Extract III	4	10	40.0±5.2

a: The inhibition rate (%) is calculated by the following equation:

$$\frac{[(\text{score of control animal}) - (\text{score of experimental animal})]}{(\text{score of control animal})} \times 100\%$$

All the ulcer scores of the control rats were 4.

The results of pharmacological assessment shown in Tables 1 and 2 reveal that American ginseng extracts of the present invention possess excellent inhibition effects of gastric ulcers induced by stress and alcohol. In addition, according to the present invention, the American ginseng extracted with water or ethanol solution and further treated by ultrafiltration, dialysis, precipitation with ethanol, or

reverse phase chromatography, possesses excellent anti-peptic ulcer effects.

While the invention has been particularly shown and described with the reference to the preferred embodiment
5 thereof, it will be understood by those skilled in the art that various changes in form and details may be made without departing from the scope of the invention.

WHAT IS CLAIMED IS:

- 1 1. A pharmaceutical composition for preventing and/or
2 treating peptic ulcer, comprising:
 - 3 (i) an effective amount of American ginseng and/or the
4 extract thereof; and
 - 5 (ii) a physiologically or pharmaceutically acceptable
6 carrier or excipient.
- 1 2. The pharmaceutical composition according to claim 1,
2 wherein said American ginseng is *Panax quinquefolium* L..
- 1 3. The pharmaceutical composition according to claim 1,
2 wherein said American ginseng extract is extracted with a
3 solvent having a polarity higher than 0.88.
- 4 4. The pharmaceutical composition according to claim 3,
5 wherein said American ginseng extract is extracted with 10%
6 ~ 80% ethanol aqueous solution.
- 1 5. The pharmaceutical composition according to claim 3,
2 wherein said American ginseng extract is extracted with
3 water.
- 1 6. The pharmaceutical composition according to claim 1,
2 wherein said American ginseng extract is extracted with
3 water or 10% ~ 80% ethanol aqueous solution, centrifuged,
4 and filtered through an ultrafiltration membrane with
5 molecular weight cut off 1,000 to give a retentate
6 containing substances with molecular weight greater than

7 1,000 dalton, and the retentate being concentrated to give
8 an extract I.

1 7. The pharmaceutical composition according to claim 6,
2 wherein said American ginseng extract is extracted with
3 water or 10% ~ 80% ethanol aqueous solution, centrifuged,
4 and filtered through an ultrafiltration membrane with
5 molecular weight cut off 1,000 to give a filtrate containing
6 substances with molecular weight less than 1,000 dalton, the
7 filtrate being concentrated to dryness, ethanol solution is added
8 to dissolve said substances, said ethanol solution is filtered
9 to obtain a soluble portion, said soluble portion is added into
10 said extract I as claimed in claim 6 to obtain a mixture,
11 and said mixture is concentrated to give an extract II.

1 8. The pharmaceutical composition according to claim 1,
2 wherein said American ginseng extract is extracted with
3 water or 10% ~ 80% ethanol aqueous solution, centrifuged,
4 filtered through an ultrafiltration membrane with molecular
5 weight cut off 3,000 to give a retentate containing
6 substances with molecular weight greater than 3,000 dalton,
7 and the retentate being concentrated to give an extract III.

1 9. The pharmaceutical composition according to claim 8,
2 wherein said American ginseng extract is extracted with
3 water or 10% ~ 80% ethanol aqueous solution, centrifuged,
4 filtered through an ultrafiltration membrane with molecular
5 weight cut off 3,000 to give a filtrate containing
6 substances with molecular weight less than 3,000 dalton, the
7 filtrate being loaded onto a reverse phase column, eluted
8 with water, followed by 95% ethanol solution and the

9 eluate is collected, and then the 95% ethanol eluate is combined with said
10 extract III in claim 8 and concentrated to give extract IV.

1 10. The pharmaceutical composition according to claim 1,
2 wherein said American ginseng extract is extracted with 30%
3 ~ 90% ethanol aqueous solution followed by filtration and
4 concentration to give extract V.

1 11. The pharmaceutical composition according to claim 1,
2 wherein said peptic ulcer is a gastric ulcer or duodenal
3 ulcer.

1 12. A process of preparing American ginseng and/or an extract thereof
2 for preventing and/or treating peptic ulcers, comprising the
3 steps of:

4 (a) treating American ginseng with a solvent with a
5 polarity higher than 0.88 to obtain an extract;

6 (b) filtering said extract to obtain a filtrate; and

7 (c) centrifuging said filtrate and collecting the
8 supernatant to give the total extract.

1 13. The process according to claim 12, further
2 comprising the step of ultrafiltrating said total extract to
3 give a retentate and a filtrate.

1 14. The process according to claim 13, wherein said
2 ultrafiltrating is a step in which said total extract is
3 filtered by means of an ultrafiltration membrane with
4 molecular weight cut off 1,000 or 3,000 to remove smaller
5 molecules.

1 15. The process according to claim 12, further
2 comprising the step of dialyzing said total extract.

1 16. The process according to claim 15, wherein said
2 dialyzing is a step in which said total extract is dialyzed
3 by means of a dialysis membrane with molecular weight cut
4 off 500 to remove smaller molecules.

1 17. The process according to claim 13, further
2 comprising a precipitating step in which said filtrate is
3 concentrated to dryness and then dissolved with 50% ~ 100%
4 ethanol to obtain the soluble portion.

1 18. The process according to claim 13, further
2 comprising the step of performing reverse phase
3 chromatography of said filtrate.

1 19. The process according to claim 18, wherein said
2 reverse phase chromatography is performing with a reverse
3 phase polyaromatic resin column.

1 20. The process according to claim 12, wherein said
2 American ginseng extract is extracted with 10% ~ 80% ethanol
3 aqueous solution.

1 21. The process according to claim 12, wherein said
2 American ginseng extract is extracted with water.

22. Use of a pharmaceutical composition as claimed in any one of claims 1 to 11 in the preparation of a medicament containing an effective amount of American ginseng and/or an extract thereof for the treatment of peptic ulcer in a mammal.

23. A pharmaceutical composition substantially as described herein.

24. A process of preparing American ginseng and/or an extract thereof substantially as described herein.

Amendments to the claims have been filed as follows

WHAT IS CLAIMED IS:

1 1. A pharmaceutical composition for preventing and/or
2 treating peptic ulcer, comprising:
3 (i) an effective amount of American ginseng and/or the
4 extract thereof; and
5 (ii) a physiologically or pharmaceutically acceptable
6 carrier or excipient.

1 2. The pharmaceutical composition according to claim 1,
(2 wherein said American ginseng is *Panax quinquefolium* L..

1 3. The pharmaceutical composition according to claim 1,
2 wherein said American ginseng extract is extracted with a
3 solvent having a polarity higher than 0.88.

4 4. The pharmaceutical composition according to claim 3,
5 wherein said American ginseng extract is extracted with 10%
6 ~ 80% ethanol aqueous solution.

1 5. The pharmaceutical composition according to claim 3,
(2 wherein said American ginseng extract is extracted with
3 water.

1 6. The pharmaceutical composition according to claim 1,
2 wherein said American ginseng extract is extracted with
3 water or 10% ~ 80% ethanol aqueous solution, centrifuged,
4 and filtered through an ultrafiltration membrane with
5 molecular weight cut off 1,000 to give a retentate
6 containing substances with molecular weight greater than

7 1,000 dalton, and the retentate being concentrated to give
8 an extract I.

1 7. The pharmaceutical composition according to claim 6,
2 wherein said American ginseng extract is extracted with
3 water or 10% ~ 80% ethanol aqueous solution, centrifuged,
4 and filtered through an ultrafiltration membrane with
5 molecular weight cut off 1,000 to give a filtrate containing
6 substances with molecular weight less than 1,000 dalton, the
7 filtrate being concentrated to dryness, ethanol solution is added
8 to dissolve said substances, said ethanol solution is filtered
9 to obtain a soluble portion, said soluble portion is added into
10 said extract I as claimed in claim 6 to obtain a mixture,
11 and said mixture is concentrated to give an extract II.

1 8. The pharmaceutical composition according to claim 1,
2 wherein said American ginseng extract is extracted with
3 water or 10% ~ 80% ethanol aqueous solution, centrifuged,
4 filtered through an ultrafiltration membrane with molecular
5 weight cut off 3,000 to give a retentate containing
6 substances with molecular weight greater than 3,000 dalton,
7 and the retentate being concentrated to give an extract III.

1 9. The pharmaceutical composition according to claim 8,
2 wherein said American ginseng extract is extracted with
3 water or 10% ~ 80% ethanol aqueous solution, centrifuged,
4 filtered through an ultrafiltration membrane with molecular
5 weight cut off 3,000 to give a filtrate containing
6 substances with molecular weight less than 3,000 dalton, the
7 filtrate being loaded onto a reverse phase column, eluted
8 with water, followed by 95% ethanol solution and the

9 eluate is collected, and then the 95% ethanol eluate is combined with said
10 extract III in claim 8 and concentrated to give extract IV.

1 10. The pharmaceutical composition according to claim 1,
2 wherein said American ginseng extract is extracted with 30%
3 ~ 90% ethanol aqueous solution followed by filtration and
4 concentration to give extract V.

1 11. The pharmaceutical composition according to claim 1,
2 wherein said peptic ulcer is a gastric ulcer or duodenal
3 ulcer.

1 12. A process of obtaining American ginseng extract for a
2 pharmaceutical composition as claimed in claim 1 for preventing and/or
3 treating peptic ulcers, comprising the steps of:

4 (a) treating American ginseng with a solvent with a
5 polarity higher than 0.88 to obtain an extract;

6 (b) filtering said extract to obtain a filtrate; and

7 (c) centrifuging said filtrate and collecting the
8 supernatant to give the total extract.

1 13. The process according to claim 12, further
2 comprising the step of ultrafiltrating said total extract to
3 give a retentate and a filtrate.

1 14. The process according to claim 13, wherein said
2 ultrafiltrating is a step in which said total extract is
3 filtered by means of an ultrafiltration membrane with
4 molecular weight cut off 1,000 or 3,000 to remove smaller
5 molecules.

1 15. The process according to claim 12, further
2 comprising the step of dialyzing said total extract.

1 16. The process according to claim 15, wherein said
2 dialyzing is a step in which said total extract is dialyzed
3 by means of a dialysis membrane with molecular weight cut
4 off 500 to remove smaller molecules.

1 17. The process according to claim 13, further
(2 comprising a precipitating step in which said filtrate is
3 concentrated to dryness and then dissolved with 50% ~ 100%
4 ethanol to obtain the soluble portion.

1 18. The process according to claim 13, further
2 comprising the step of performing reverse phase
3 chromatography of said filtrate.

1 19. The process according to claim 18, wherein said
2 reverse phase chromatography is performing with a reverse
3 phase polyaromatic resin column.

(1 20. The process according to claim 12, wherein said
2 American ginseng extract is extracted with 10% ~ 80% ethanol
3 aqueous solution.

1 21. The process according to claim 12, wherein said
2 American ginseng extract is extracted with water.

22. Use of a pharmaceutical composition as claimed in any one of claims 1 to 11 in the preparation of a medicament containing an effective amount of American ginseng and/or an extract thereof for the treatment of peptic ulcer in a mammal.

23. A pharmaceutical composition substantially as described herein with reference to claim 1.

24. A process of preparing American ginseng and/or an extract thereof substantially as described herein with reference to claim 12.



INVESTOR IN PEOPLE

Application No: GB 0017046.4
Claims searched: 1-24

Examiner: Annabel Ovens
Date of search: 11 January 2001

Patents Act 1977 Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.S): A5B (BE, BKC)

Int Cl (Ed.7): A61K 35/78; A61P 1/04

Other: Online: PAJ, EPODOC, WPI, TXTE, NAPRALERT

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	WO 99/30725 A1 (C. V. TECHNOLOGIES INC.) see page 4 lines 15-19, page 7 line 4-page 10 line 5 and Table 5	1-24
X	US 5071839 (YAGUANG LIU) see whole document	1-21, 23 and 24
X	US 4945115 (YAGUANG LIU) see whole document	1-21, 23 and 24
X	US 4795742 (YAGUANG LIU) see whole document	1-21, 23 and 24
X	US 4708949 (YAGUANG LIU) see whole document	1-21, 23 and 24

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Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.